CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Executive Director, Proprietary Regulatory Affairs
417 Wakara Way
Salt Lake City, UT 84108

Dear Ms. Frank:

Please refer to your new drug application (NDA) dated January 12, 2001, received January 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alora (estradiol transdermal system) 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

Your submission of February 5, 2002, constituted a complete response to our January 18, 2002, action letter.

This new drug application provides for 1) addition of a 0.025 mg/day strength product and 2) addition of an indication for the prevention of postmenopausal osteoporosis for all strengths.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert) and submitted draft labeling (pouch and carton labels submitted on November 15, 2001). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-310." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA, NDA 20-655, for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Samuel Y. Wu, Pharm.D., Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

David Orloff
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

NOV 16 2001

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs
Research Park
417 Wakara Way
Salt Lake City, UT 84108

Dear Ms. Frank:

Please refer to your new drug application (NDA) dated January 12, 2001, received January 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alora (estradiol transdermal system) 0.025 mg/day, 0.05 mg/day, and 0.075 mg/day.

We acknowledge receipt of your submissions dated February 14, May 11, September 26, October 16 and 19, and November 7, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert, text for the patient package insert). In addition, submit a copy of your proposed container and pouch label.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Samuel Y. Wu, Pharm.D., Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

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Labeling

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/s/

David Orloff
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

Watson Laboratories, Inc.
Attention: Dorothy Frank, M.S., R.A.C.
Director, Regulatory Affairs
Research Park
417 Wakara Way
Salt Lake City, UT 84108

JAN 18 2002

Dear Ms. Frank:

Please refer to your new drug application (NDA) dated January 12, 2001, received January 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alora (estradiol transdermal system) 0.02 5mg/day, 0.05 mg/day, and 0.075 mg/day.

We acknowledge receipt of your submissions dated January 14 and 16, 2002. Your submission of November 19, 2001, constituted a complete response to our November 16, 2001, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following labeling issues:

1. The table regarding vasomotor symptoms cannot be verified. To support Table 3, "Mean Change from Baseline in Frequency of Moderate-to-Severe Vasomotor Symptoms for **Alora** Compared to Placebo," submit the efficacy data from the placebo-controlled clinical trial (E94001). These data should be provided in SAS transport format according to the Guidance for Industry, entitled, "Providing Regulatory Submissions in Electronic Format-NDAs." Data should include values at baseline and weeks 4, 8 and 12, utilizing the last observation carried forward (LOCF) data imputation method. A data flag should be used to indicate any imputed value.

2. The graph provided by the Agency in figure 3 is an example of the presentation requested for that figure, "Mean % change in BMD from baseline at 1 and 2 years after initiation of therapy with placebo and Alora 0.025. 0.05 and 0.075 mg/day." A new graph using the corrected numbers in the completer and ITT populations should be generated.

In addition, it will be necessary for you to submit draft labeling for the drug. Revisions have been incorporated directly into the enclosed labeling (text for the package insert, text for the patient package insert). Additions have been noted with underlining, deletions have been noted as ~~strikeouts~~. Additional comments requiring response are in **14 pt bold face type.**

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Samuel Y. Wu, Pharm.D., Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
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for Dr. Orloff

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Labeling